REMARKS/ARGUMENTS

Support for the amendment to claims 1, 3, and 8-11, i.e., replacing "detecting" with "assaying" and "detected" with "assayed" may be found implicitly and inherently[1] throughout the specification. For example, the specification discloses numerous assay formats one may use to identify proteins on page 7, e.g., enzyme immunoassay, radioimmunoassay, Western blot analysis and ELISA, and numerous assay formats one may use to identify mRNA on page 3, e.g, RT-PCR, Q-PCR, Northern and other hybridization methods. The act of using such assays would be referred to as "assaying" (when using active voice) and "assayed" (when using passive voice), and therefore this amendment to the claims does not constitute new matter.

Support for the amendment to claim 3, step a), may be found on page 3 of the originally-filed application, which describes changes in expression profiles from a baseline profile while the transplanted patient is exposed to therapy (e.g., certain drug treatments for CR). New claims 15-18 find support on page 4, wherein the level of mRNA or protein encoded is preferably detected within 4 to 7 months post-transplantation, e.g., 6 months post-transplantation. Support for the 6 month time point in claims 16 and 18 may also be found in, e.g., Tables 1-3, which provide genes differentially displayed in pre-chronic rejection ("CR") subjects versus control subjects at 6 months post transplant. Upon entrance of the instant Amendment, claims 1-3, 8-11 and 15-18 will be pending and under examination.

Applicants wish to thank the Examiner for acknowledging the priority benefit to U.S. Provisional Application 60/405,225.

Applicants also wish to thank the Examiner for withdrawing the previous 35 U.S.C. §§102 and 103 rejections.

Rejections Under 35 U.S.C. §112, First Paragraph – Enablement

The Examiner has rejected claims 1-4 and 8-11 under 35 U.S.C. §112, first paragraph, as allegedly failing to comply with the enablement requirement. Claim 4 has been cancelled, rendering this rejection moot.

On page 3, the Examiner alleges that claim 3 reads upon the use of any tissue sample. Claim 3 has been amended to clarify that the tissue biopsy samples in steps a and c are from renal allografts.

[1] An adequate description may be made in any way through express, implicit, or even inherent disclosures in the application, including words, structures, figures, diagrams, and/or formulae. (MPEP §§ 2163(I)(B)).

On page 3, the Examiner argues that the specification does not provide and explicit definition for "corresponding to" SEQ ID NOs:29-38. Claims 1 and 3 have been amended to remove the phrase "corresponding to".

On page 4, the Examine argues that the phrase "CR-inhibiting agent" defines a class of compounds based primarily on function. Claim 3 has been amended to remove the phrase "CR-inhibiting agent".

On page 4, the Examiner argues that the claims encompass the detection of SEQ ID NOs:35 and 36 by real time Q-PCR, but the specification teaches that insufficient data prevented the use of these methods for AL049449 and W26469. Applicants note that Table 3 on page 21 clearly shows that AL049449 was identified by Q-PCR. Moreover, while Applicants did not identify W26469 by Q-PCR in the instant application, one of ordinary skill in the art would certainly be able to do so without any undue experimentation. Using, e.g., the sequence for W26469 found in GenBank® (and set forth in SEQ ID NO:36), one of ordinary skill in the art could design primers for Q-PCR, or, alternatively, could sequence the entirety of W26469, and use such sequence information for routine primer design. Routine gene sequencing and routine primer design are both well within the skill of one or ordinary skill in the art, and do not require any undue experimentation.

On page 6 of the Office Action, the Examiner argues that the phrase "a negative indication of CR in the kidney transplanted subject" could be read as the absence of CR or an undesirable outcome. Claim 3 has been amended to clarify that comparing step e is used to indicate an increased likelihood of developing CR.

On page 5 of the Office Action, the Examiner argues that the unpredictability allegedly set forth by Damrauer (of record) is not addressed by the instant application. Specifically, the Examiner argues

> The specification teaches that RNA was collected at three time points: at the time of transplantation (baseline), 6 months after transplantation, and 12 months after transplantation (e.g., page 9, 1st full paragraph). The specification does not teach which time points were used in the classification of the 17 transplant patients. The specification only envisions comparing the baseline of a control sample to a test sample (e.g., pages 3-4). The specification does not teach the comparison of a test sample taken at 6 months post-transplant to the expression data obtained from a population of control samples, where the control sample was obtained at 6 months post-transplant, and the control individuals do not develop chronic rejection. However, the post-filing

art teaches that this comparison at the 6 moth post-transplantation time point is what is required to use the claimed 10 genes as a predictor of chronic rejection (Scherer et al. Transplantation, Vol. 75, No. 8, pages 1323-1330, April 2003; e.g., page 1326, Results). Guidance with respect to selecting the 6 month post-transplantation time point for the control samples is lacking in the instant specification. Furthermore, the specification does not provide any evidence that the

For the following reasons, and the reasons discussed extensively in the previous response, Applicants respectfully traverse this rejection.

First, Scherer et al. does not state that a comparison must be done using six month biopsy samples. It is simply the case that the comparison in Scherer et al. was, in fact, done at 6 months. However, there is nothing in Scherer et al. that states or even suggests that comparisons using different, including earlier, biopsy time points would not work. The focus of Scherer et al. is that the gene set disclosed therein may be used to predict CR at an earlier time point than would otherwise have been possible using existing techniques/genes sets (see, e.g., the beginning of the Discussion section of Scherer et al., especially the second paragraph: "To our knowledge, no biomarker has so far ... normal post-operative range"). Thus, contrary to what the Office alleges, Scherer et al. does not teach that comparison at the 6 month time point is required to use the genes of Table 3 as markers of CR.

Second, the Office is mistaken in the allegation that the specification does not provide guidance with respect to selecting a 6 month post-transplantation time point for control samples. Table 3 of the specification indicates that comparison was made at 6 months post-transplantation, e.g., "upregulated in preCR group at month 6". Indeed, the Table 3 descriptor on page 21 indicates that table provides "the most significant differential expression patters for the pre-CR and the control group." Page 18 of the application states "[o]ne group of patients developed CR within 6 months after *the* timepoint the biopsy was taken, the other group did not." (emphasis added). This reference is to the 17 transplant patients monitored for CR, from whom biopsies were used to identify the gene sets of Tables 1-3. The sentence indicates that the comparison was undertaken with biopsies from a single time point (i.e., "*the* timepoint"), which, given the subtitles and description of Table 3 (e.g., "upregulated in preCR group at month 6"), is clearly 6 month biopsy samples.

Page 18 of the application, last paragraph, gives the demographic and clinical characteristics of all the 17 patients in the study that led to the identification of the gene classifiers. This paragraph cross refers to Table 5 on page 23 - which Table states that recipients A-I developed CR between month 6 and month 12, whereas patients J-Q remained healthy. The logical reading of the specification is that all the biopsies used to identify the gene

sets of Tables 1-3 were taken and tested at 6 months when no rejections were apparent; the first group (A-I) went on to develop CR between 6 and 12 months (i.e. within 6 months of the biopsies), whereas the other, control group, did not. This is entirely consistent with the time periods mentioned in the Scherer et al. reference, which is the scientific publication of the instant application. Scherer et al. states "[w]e exploited gene-chip technology to identify genes with differential expression patterns in renal - protocol biopsies that were taken from a cohort of 17 patients with functional grafts and normal postoperative clinical and histologic parameters 6 months before 9 of these patients developed CR." (Scherer et al., p. 1323; see also Scherer et al. at Fig. 2A)

Third, as for the nature of a control, it would be readily apparent to a person skilled in the art that a control would typically be a sample taken at a clinically relevant timepoint from a patient who does not eventually develop CR and that the ideal comparison is between samples taken at the same time post-transplantation. This is simply scientific procedure and is certainly implied from page 18, Table 3 and Table 5. In fact, in the absence of any evidence to the contrary, one would logically understand that all samples used to generate the gene sets from Tables 1-3 are from the same timepoint (6 months post-transplantation) and that the reference to "upregulated in preCR group at month 6" and "downregulated in preCR group at month 6" could only be with reference to a comparison with samples taken at the same timepoint from patients who did not eventually develop CR.

For at least the above reasons, Applicants submit the pending claims satisfy the enablement requirement of 35 U.S.C. §112, first paragraph. Applicants therefore respectfully request withdrawal of the outstanding enablement-based rejections.

Rejections Under 35 U.S.C. §112, First Paragraph – Written Description

The Examiner has rejected claims 1-4 and 8-11 under 35 U.S.C. §112, first paragraph, as allegedly failing to comply with the written description requirement. Claim 4 has been cancelled, rendering this rejection moot.

On page 8, the Examiner argues that there is no evidence that Applicants possessed a representative number of sequences "corresponding to" SEQ ID NOs:29-38, nor is there evidence that sequences "corresponding to" SEQ ID NO:36 were known in the art at the time the invention was made. Claims 1 and 3 have been amended to remove the phrase "corresponding to".

On page 8, the Examine argues that the phrase "CR-inhibiting agent" defines a class of compounds based primarily on function. Claim 3 has been amended to remove the phrase "CR-inhibiting agent".

For at least the above reasons, Applicants submit the pending claims satisfy the written description requirement of 35 U.S.C. §112, first paragraph. Applicants therefore respectfully request withdrawal of the outstanding the written description-based rejections.

CONCLUSION

In light of the above amendments, observations and remarks, Applicants respectfully submit that the presently claimed invention satisfies 35 U.S.C. §112, and is neither disclosed nor suggested by any art of record. Accordingly, reconsideration and allowance of all claims in this application is earnestly solicited.

Applicants' undersigned attorney may be reached in our New Jersey office by telephone at (862) 778-9308. All correspondence should continue to be directed to our below-listed address.

Respectfully submitted,

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